SMCHD1 gene

structural maintenance of chromosomes flexible hinge domain containing 1

Normal Function

The *SMCHD1* gene provides instructions for making a protein that is involved in regulating gene activity by altering the structure of DNA. Specifically, the SMCHD1 protein plays a role in DNA methylation, which is the addition of methyl groups (consisting of one carbon atom and three hydrogen atoms) to DNA molecules. The addition of methyl groups turns off (silences) genes, so hypermethylated regions of DNA tend to have fewer genes that are turned on (active).

The SMCHD1 protein is involved in a process called X-inactivation or Lyonization. Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than egg cells. X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. The SMCHD1 protein helps to inactivate the X chromosome by hypermethylating certain areas of DNA called CpG islands. The protein then remains attached (bound) to the inactive X chromosome to help keep it inactivated throughout life.

The SMCHD1 protein also plays a role in hypermethylation of a region near the end of chromosome 4 called D4Z4. This region consists of 11 to more than 100 repeated segments, each of which is about 3,300 DNA base pairs (3.3 kb) long. The segment closest to the end of chromosome 4 contains a gene called *DUX4*. Because the D4Z4 region is hypermethylated, the *DUX4* gene is silenced in most adult cells and tissues. Little is known about the function of the protein produced from the *DUX4* gene; it appears to help control the activity of other genes.

Studies suggest that the *SMCHD1* gene is also involved in repairing damaged DNA. However, little is known about its role in this process.

Health Conditions Related to Genetic Changes

facioscapulohumeral muscular dystrophy

More than a dozen mutations in the *SMCHD1* gene have been found to cause facioscapulohumeral muscular dystrophy, a disorder characterized by muscle weakness and wasting (atrophy) that worsens slowly over time. Two forms of the disorder have been described: type 1 (FSHD1) and type 2 (FSHD2). Changes in the *SMCHD1* gene appear to play a role in both types.

SMCHD1 gene mutations cause most cases of FSHD2. These mutations reduce the amount of SMCHD1 protein available to add methyl groups to the D4Z4 region.

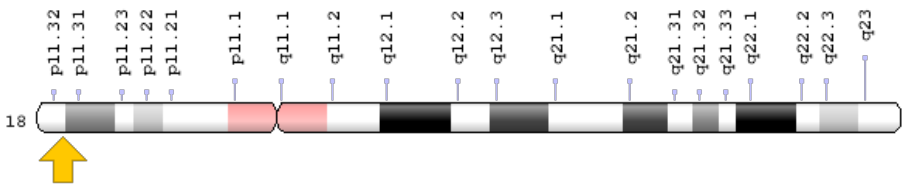
The resulting hypomethylation of this region prevents the *DUX4* gene from being silenced in cells and tissues where it is usually turned off, such as adult muscle cells. However, hypomethylation of the D4Z4 region results in facioscapulohumeral muscular dystrophy only when it occurs in people who also have at least one copy of chromosome 4 that is described as "permissive." A "permissive" chromosome 4 has a functional region of DNA known as a pLAM sequence located next to the *DUX4* gene. The pLAM sequence is necessary for the production of the DUX4 protein. (Conversely, a "non-permissive" chromosome 4 does not contain a functional pLAM sequence, preventing the production of any DUX4 protein.) Researchers believe that the DUX4 protein influences the activity of other genes, particularly in muscle cells. However, it is unknown how the presence of this protein damages or destroys these cells, leading to progressive muscle weakness and atrophy.

Studies suggest that mutations in the *SMCHD1* gene can increase the severity of disease in people with the other type of facioscapulohumeral muscular dystrophy, FSHD1. FSHD1 results when the D4Z4 region is abnormally shortened (contracted), containing between 1 and 10 repeats instead of the usual 11 to 100 repeats. Researchers suspect that the combination of a contracted D4Z4 region and a *SMCHD1* gene mutation causes the D4Z4 region to have even fewer methyl groups attached, which allows the *DUX4* gene to be highly active. In people with both genetic changes, the overactive gene leads to severe muscle weakness and atrophy.

Chromosomal Location

Cytogenetic Location: 18p11.32, which is the short (p) arm of chromosome 18 at position 11.32

Molecular Location: base pairs 2,655,887 to 2,805,017 on chromosome 18 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- KIAA0650
- SMC hinge domain-containing protein 1
- structural maintenance of chromosomes flexible hinge domain-containing protein 1

Additional Information & Resources

Educational Resources

- Developmental Biology (sixth edition, 2000): Methylation Pattern and the Control of Transcription
  https://www.ncbi.nlm.nih.gov/books/NBK10038/
- Madame Curie Bioscience Database (2010): X Chromosome Inactivation and Embryonic Stem Cells
  https://www.ncbi.nlm.nih.gov/books/NBK45037/

GeneReviews

- Facioscapulohumeral Muscular Dystrophy
  https://www.ncbi.nlm.nih.gov/books/NBK1443

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28SMCHD1%5BTIAB%5D%29+OR+%28structural+maintenance+of+chromosomes+flexible+hinge+domain+containing+1%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

OMIM

- STRUCTURAL MAINTENANCE OF CHROMOSOMES FLEXIBLE HINGE DOMAIN-CONTAINING PROTEIN 1
  http://omim.org/entry/614982

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_SMCHD1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SMCHD1%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=29090
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/23347
- UniProt
  http://www.uniprot.org/uniprot/A6NHR9

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